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Absorption and Bioavailability of Oral Transmucosal Fentanyl Citrate

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Oral transmucosal fentanyl citrate (OTFC) is a novel, noninvasive dosage form of fentanyl used to provide children and adults with sedation, anxiolysis, and analgesia. In order to determine the bioavailability and absorption of fentanyl from OTFC, 12 volunteers were given intravenous fentanyl citrate or OTFC 15 μg/kg on each of two occasions. On a third occasion, the authors assessed oral administration (gastrointestinal absorption) by giving eight of the same volunteers the same dose of a solution of fentanyl citrate to swallow. In each study, arterial blood samples were taken over 24 h for analysis of plasma fentanyl. After intravenous (iv) administration of fentanyl, clearance (mean ± standard deviation) was 0.67 ± 0.15 l/min; volume of distribution at steady state was 287 ± 79 l; and the terminal elimination half-life was 425 ± 102 min. Peak plasma concentrations of fentanyl were higher (3.0 ± 1.0 *vs.* 1.6 ± 0.6 ng/ml, $P = 0.01$) and occurred sooner (22 ± 2.5 *vs.* 101 ± 48.8 min, $P = 0.003$) after OTFC than after oral solution administration. Plasma concentrations of fentanyl after OTFC decreased rapidly, to less than 1.0 ng/ml within 75–135 min after the beginning of administration. Peak absorption rate was greater (11.1 ± 4.3 *vs.* 3.6 ± 2.1 μg/min, $P = 0.004$) and occurred much sooner after OTFC than after oral solution administration (19 ± 2.6 *vs.* 87.5 ± 38.1 min, $P = 0.001$). Systemic bioavailability was greater after OTFC administration than after the oral solution (0.52 ± 0.1 *vs.* 0.32 ± 0.1, $P = 0.01$). Terminal elimination half-life was similar after all modes of fentanyl delivery—OTFC (460 ± 313 min), iv (425 ± 102 min), or oral solution (469 ± 123 min). These results suggest that although absorption of fentanyl from OTFC occurs through both the oral mucosa and the gastrointestinal tract, it is more rapid at the former. The data also indicate that sequestration of fentanyl in the oral mucosa is minimal. (Key words: Analgesia, postoperative. Anesthetics, fentanyl: bioavailability. Anesthetic techniques, transmucosal: fentanyl. Pharmacokinetics: fentanyl.)

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ORAL TRANSMUCOSAL FENTANYL CITRATE (OTFC) is a novel, noninvasive dosage form of fentanyl used to provide children and adults with sedation, anxiolysis, and analgesia.[1–3] OTFC units consist of a lozenge with a handle and are of uniform size and shape. They are made by dissolving fentanyl citrate in a sucrose solution that is poured into a mold and allowed to harden on a handle. In the mouth, the unit dissolves in saliva: a portion of the fentanyl diffuses across the oral mucosa, and the rest is swallowed and partially absorbed in the stomach and intestine. In theory, oral mucosal absorption of fentanyl should be rapid, since the molecular size of fentanyl is small and the drug is highly lipid-soluble. However, to date, no pharmacokinetic data exist for fentanyl administration using this new delivery system. Therefore, our study was designed to determine the absorption and bioavailability of OTFC in adult volunteers. To characterize gastrointestinal absorption of fentanyl, a similar analysis was performed after some of the same volunteers had swallowed an oral solution of fentanyl citrate.

Materials and Methods

Approval was obtained from the Human Institutional Review Board of the University of Utah Medical Center, and informed written consent was obtained from 12 healthy adult male volunteers. Subjects were nonsmokers, 23–31 yr of age, who deviated no more than 15% from ideal body weight (68–85 kg); they had no history of drug or ethanol abuse and were not taking any pain medications.

In a randomized crossover fashion, subjects were given 15 μg/kg of fentanyl during each 24-h study session either by the iv or by the oral transmucosal route. That is, in the first study session, half of the volunteers were given iv fentanyl, and the other half, OTFC. Eight of the original 12 volunteers returned for a third session, at which time they swallowed an oral solution of fentanyl (hereafter called "oral administration" and "oral fentanyl"). All three sessions were completed within 3–4 months.

Subjects fasted overnight prior to each study session. At the start of each study session, a peripheral 18-G iv catheter was inserted for maintenance fluid administration (lactated Ringer's solution at the rate of 1.5 $ml \cdot kg^{-1} \cdot h^{-1}$), and a 20-G catheter was inserted into the radial artery for blood sampling. Additional monitors included a noninvasive automatic blood pressure cuff, a pulse oximeter and an electrocardiogram.

The three modes of fentanyl delivery were as follows. Intravenous (iv) administration consisted of a continuous infusion at the rate of 150 μg/min until a total of 15 μg/kg was given. For oral transmucosal administration, subjects were instructed to place a 15 μg/kg OTFC unit in the buccal pouch and suck on it, pacing themselves (with instruction from the investigator) so that the unit was consumed in 15 min. For oral administration, a 15-μg/kg OTFC unit was dissolved in sterile water to a total of 10 ml. Volunteers swallowed this solution, rinsed their mouths with two 5-ml aliquots of sterile water, and swallowed the rinsing water.

Finger pulse oximetry was used for continuous monitoring of each subject's hemoglobin oxygen saturation (Sp_{O_2}). Respiratory rate, systolic and diastolic arterial blood pressures, and heart rate were measured and recorded at baseline and just prior to arterial blood sampling. If Sp_{O_2} decreased to less than 90%, subjects were encouraged to take a deep breath. If Sp_{O_2} did not increase to greater than 90% after three prompts, oxygen was administered by nasal cannula at the rate of 3 l/min. If apnea or rigidity occurred, ventilation with 100% oxygen was controlled using a face mask and breathing bag. All adverse reactions were recorded.

Blood Sampling and Fentanyl Analysis

Blood samples (4 ml) were obtained from the arterial catheter at baseline and for 24 h during all three study sessions, at the following intervals. For iv administration, samples were obtained every 2 min during infusion; after infusion, they were obtained every 1 min for 10 min, every 15 min for the 1 h, and then every 2 h for 24 h. Blood samples were obtained every 5 min during OTFC consumption; after consumption, they were obtained every 2 min for 10 min, every 5 min for the next 1 h, and then every 2 h for 24 h. For oral administration, blood samples were obtained every 10 min for 2.5 h after the swallowing of the fentanyl solution, 30 min later, and then every 2 h for 24 h.

All blood samples were injected into preheparinized glass tubes and placed immediately on ice. Plasma was separated from red cells with a refrigerated centrifuge, placed in polypropylene tubes, and frozen at −20° C until analysis for fentanyl.

Plasma fentanyl concentrations were determined by radioimmunoassay using the modified technique described by Schüttler and White.[4] The assay was sensitive to 0.2 ng/ml with a coefficient of variation of 10% at 0.2 ng/ml, 4% at 0.8 ng/ml, and 2% at 1.7 ng/ml.

Pharmacokinetic Analysis

The area under the plasma fentanyl concentration *vs.* time curve after iv, OT, and oral solution administration (AUC_{iv}, AUC_{OTFC}, and AUC_{oral}, respectively) was calculated from the time of administration of fentanyl to the last measurable plasma concentration using the linear trapezoid method.[5] Extrapolation of the AUC from the time of the last measurable fentanyl concentration to infinity was calculated by dividing the last plasma concentration by the first-order rate constant of the terminal phase of the profile. This first-order rate constant was determined using linear regression on the log-transformed plasma fentanyl concentration data from the terminal log-linear phase of the plasma concentration profile. The sum of these two components was the estimate of the total AUC. The terminal elimination half-life of fentanyl was calculated from the first-order rate constant of the terminal phase of the plasma concentration *versus* time profile.

Also calculated were the other following variables: clearance, mean residence time, and volume of distribution of fentanyl at steady state using noncompartmental analysis[6]; clearance as the ratio of the iv fentanyl dose and AUC_{iv}; mean residence time, as the ratio of the area under the first moment curve of iv fentanyl concentration *versus* time data and AUC_{iv}; and volume of distribution at steady state as the product of clearance and mean residence time. The unit disposition function for fentanyl was determined using least-squares deconvolution of the plasma fentanyl concentrations from the iv portion of the study by the dosing function for the iv portion.[7] Deconvolution was done with the constraint that the resultant unit disposition function be a positive, nonincreasing function.

For the OTFC administration portion of the study, the maximum plasma concentration of fentanyl and its time of occurrence were noted from the plasma concentration *versus* time profile. The amount of fentanyl absorbed after OTFC administration was calculated as the product of fentanyl clearance (determined from the iv study) and AUC_{OTFC}. Bioavailability was calculated as the ratio of the amount of fentanyl absorbed to the amount administered. The absorption profile of OTFC was determined using least-squares deconvolution of the plasma concentrations of OTFC by the fentanyl unit disposition function. This deconvolution was performed with the constraint that the resulting absorption profile be a positive function at all time points. The total area under the absorption profile yielded a second estimate of the amount of fentanyl absorbed and hence a second estimate of bioavailability of OTFC. Data obtained from the oral fentanyl portion of the study was analyzed in a manner identical to that of the OTFC portion.

Continuous variables from the OTFC and oral solution portions of the study were compared by paired-sample *t* test and analysis of variance for repeated measures. Only matching data from the eight subjects who completed both OTFC and oral solution portions of the study were used for these comparisons. Differences were significant if $P < 0.05$. Unless otherwise stated, results are presented as mean values ± standard deviations.

TABLE 1. Terminal Elimination of Half-life of Fentanyl (min) Given by Three Routes of Administration

Subject	Intravenous	Oral Transmucosal	Oral Solution
1	402	523	434
2	348	309	497
3	913	450	ND
4	346	ND	410
5	396	691	329
6	423	384	688
7	394	468	ND
8	360	567	420
9	435	182	467
10	602	943	772
Mean* ± SD	425 ± 102	460 ± 313	469 ± 123

ND = not done; see text. *Harmonic mean.

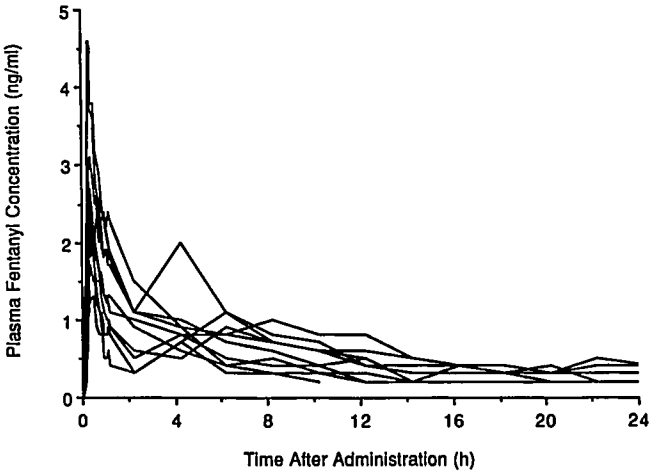

FIG. 2. Measured plasma concentrations of fentanyl for each of ten subjects who consumed OTFC 15 μg/kg.

Results

Twelve subjects completed the iv administration portion of the study, 11 the OTFC section, and 8 the oral solution section. Data from subjects 11 and 12 (iv administration) were included neither in the sample mean nor in the pharmacokinetic analysis, since the iv terminal elimination phase was not well characterized for subject 11 and since there were no matching OTFC data for subject 12 (due to inability to insert the arterial catheter). The mean age and weight of the subjects were 28 ± 2.7 yr and 76 ± 5.4 kg. The mean amount of fentanyl administered was 1,139 ± 85.4 μg. In all subjects consumption of OTFC units was completed in 15 min.

PHARMACOKINETICS

After iv infusion, clearance of fentanyl was 0.67 ± 0.15 l/min; volume of distribution at steady state was 287 ± 79 l; and terminal elimination half-life was 425 ± 102 min (table 1). Figures 1–3 show the plasma concentrations of fentanyl obtained after iv, OTFC, or oral administration, respectively, for individual subjects; figure 4 shows a comparison of the mean data of all three routes of administration. While plasma concentrations of fentanyl are approximately ten times greater after iv administration, there is no difference in terminal elimination after iv, OTFC, or oral administration (fig. 4 and table 1). Table 2 provides individual values for peak plasma concentration of fentanyl and its time of occurrence for both OTFC and oral administration. The peak plasma concentration of fentanyl was greater (3.0 ± 1.0 *vs.* 1.6 ± 0.6 ng/ml, $P = 0.01$) and occurred sooner (22 ± 2.5 *vs.* 101 ± 49 min, $P = 0.003$) after OTFC administration than after oral administration (fig. 5; Table 2). Plasma fentanyl concentrations decreased to below 1.0 ng/ml within 75–135 min after the beginning of OTFC administration (fig. 5).

Figure 6 shows the mean rates of absorption of fentanyl into the systemic circulation after OTFC and oral administration. Peak absorption rate for fentanyl was greater (11.1 ± 4.3 *vs.* 3.6 ± 2.1 μg/min, $P = 0.004$) and occurred sooner (19.0 ± 2.6 *vs.* 87.5 ± 38.1 min, $P = 0.001$) after

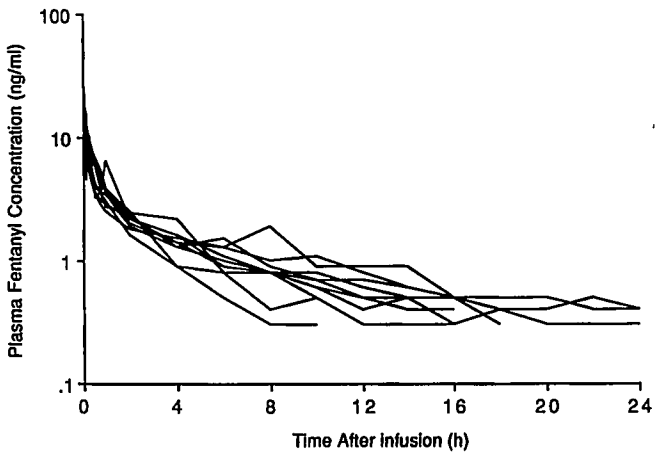

FIG. 1. Measured plasma concentrations of fentanyl for each of ten subjects who received the intravenous fentanyl infusion of 15 μg/kg.

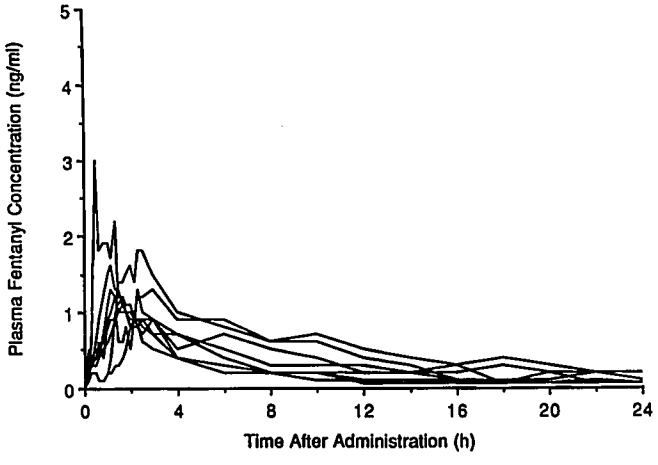

FIG. 3. Measured plasma concentrations of fentanyl for each of eight subjects given orally a solution of fentanyl 15 μg/kg.

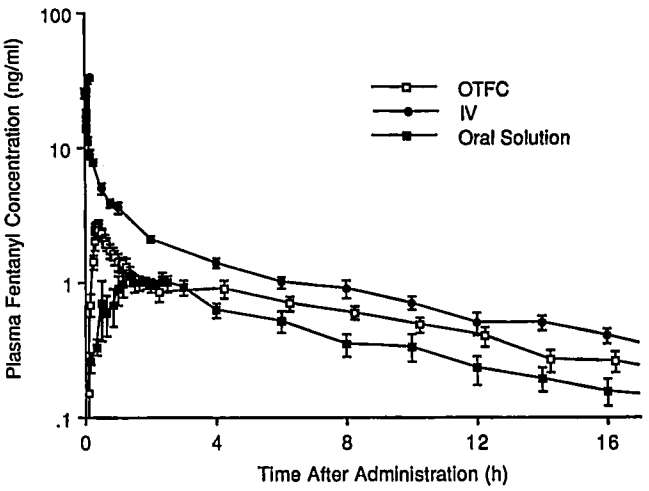

FIG. 4. Plasma concentrations of fentanyl (mean ± SEM) after intravenous (n = 10), OTFC (n = 10), or oral (n = 8) administration of fentanyl 15 μg/kg. Intravenous fentanyl was infused at a rate of 150 μg/kg; OTFC was consumed in 15 min; and the oral solution was swallowed within 10 s.

OTFC administration than after oral administration: it occurred just 4 min after the *completion* of consumption. The absorption rate of fentanyl decreased to below 1.0 μg/min (<10% of the peak) within 75–135 min of the beginning of OTFC administration.

Table 3 shows the bioavailability of OTFC and oral fentanyl, as determined by two methods (dose-normalized AUCs and area under the absorption rate *vs.* time profile). These two methods produced similar results. Mean bioavailability (by the AUC method) was greater after OTFC administration (0.52 ± 0.1) than after oral administration (0.32 ± 0.1) ($P = 0.01$). Figure 7 provides the total amount of fentanyl absorbed into the circulation over 24 h after OTFC and oral administration.

Side Effects

Although 6 of 12 (50%) subjects in the iv section of the study lost consciousness, became rigid, and required positive-pressure ventilation with 100% oxygen to keep Sp_{O_2} greater than 90%, none required paralysis or later had recall of events. The other six subjects needed supplemental oxygen and numerous prompts to breathe in order to keep Sp_{O_2} greater than 90%, but none became rigid or lost consciousness.

There were no significant differences in heart rate and systolic and diastolic blood pressure responses to iv (n = 12), OTFC (n = 11), and oral (n = 8) administration of fentanyl during the entire study. Although changes in respiratory rate after OTFC did not differ over time (0–120 min) from those found after oral administration, mean respiratory rate was significantly less at 10 min (11 ± 4 *vs.* 17 ± 4 breaths per min, $P = 0.005$) and at 20 min (11 ± 4 *vs.* 16 ± 4 breaths per min, $P = 0.05$) after OTFC administration than after oral administration. Table 4 shows the incidence of undesirable side effects after the three modes of fentanyl delivery. Urinary retention (which lasted 6 h) occurred in one subject after oral administration and in none of the subjects after iv or OTFC administration.

Discussion

Until recently, the pharmacologic management of moderate and severe pain has been limited to parenteral administration of opioid analgesics. However, innovative drug delivery devices using alternative routes of administration now are being developed to improve pain management. To understand the safe and effective use of new forms of drug administration such as OTFC, one must understand the biopharmaceutic characteristics of these delivery systems.

With iv administration, the dose is known exactly, and input into the body is instantaneous. Therefore, the rate and extent of drug distribution and elimination can easily be estimated. With non-iv drug administration, however, absorption, distribution, and elimination occur simultaneously. It is not possible to distinguish among the three

TABLE 2. Peak Plasma Concentrations of Fentanyl and Their Time of Occurrence after OTFC and Oral Solution Administration

	C_{max} (ng/ml)		T_{max} (min)	
Subject	OTFC	Oral Solution	OTFC	Oral Solution
1	2.5	1.8	21	140
2	3.1	3.0	24	30
3	4.3	1.3	19	140
4	1.4	ND	21	ND
5	2.6	1.3	25	180
6	2.8	1.6	19	70
7	2.0	ND	30	ND
8	2.7	1.1	24	100
9	4.6	1.2	21	80
10	1.7	1.3	25	70
Mean ± SD	2.8 ± 1.0	16 ± 0.6	23.0 ± 3.4	101.3 ± 48.8

C_{max} = peak plamsa concentration; T_{max} = time of occurrence of C_{max}; ND = not done.

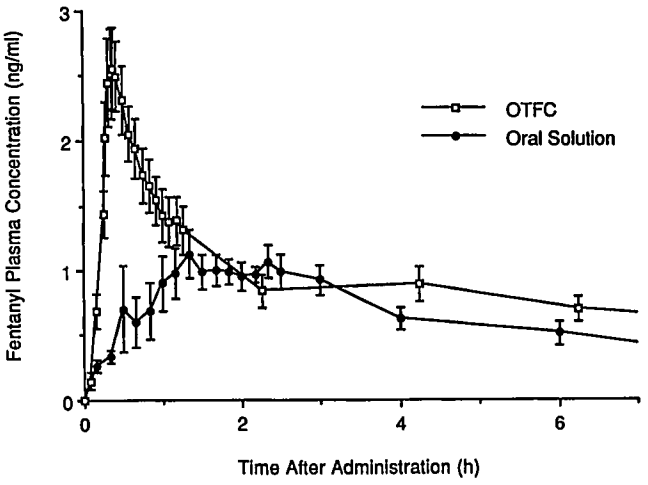

FIG. 5. Plasma concentrations of fentanyl (mean ± SEM) after OTFC or oral administration for the eight subjects who completed these sections of the study. OTFC was consumed in 15 min, and the oral solution was swallowed within 10 s.

processes when examining the curve for plasma concentration of fentanyl *vs.* time. By studying the pharmacokinetics of iv administration on one occasion and the pharmacokinetics of an alternative route of administration on another, it becomes possible to use mathematical approaches (deconvolution) to extract the true profile for absorption from that of distribution and elimination. It is not accurate to estimate absorption using iv and non-iv studies from different individuals (*i.e.*, using previously determined iv population kinetics for the deconvolution of currently determined plasma concentrations after OTFC administration).[8] Instead, it is necessary to use the same individual for both iv and non-iv administrations and to assume that distribution and elimination remain the same between studies. Only by using stable isotope techniques can iv and an alternate route of drug delivery be studied simultaneously in the same individual.

Absorption of fentanyl after oral transmucosal administration first involves entry of the drug into the body through the oral mucosa and then absorption of the fentanyl swallowed in saliva through the gastrointestinal tract. Thus, our study design used the same individual for iv, OTFC, and oral administration to determine and contrast absorption after non-iv routes of administration.

Our pharmacokinetic data from iv studies are comparable to those in the literature, despite the use of different techniques for analyzing the pharmacokinetic data.[9-11] Noncompartmental statistical moment theory does not require that the pharmacokinetic data be fit to a specific one-, two-, or three-compartmental model. The only required assumption is that the pharmacokinetic relationships are linear, *i.e.*, that a change in the dose of drug administered produces a proportional change in plasma concentration. In addition, noncompartmental analysis avoids the problems associated with nonlinear regression and does not force the data to fit preconceived pharmacokinetic models. The results are derived directly from the data rather than from curve "fits" that only approximate the data.

One assumption critical to the analysis of our data is that the distribution and elimination characteristics of fentanyl for an individual subject would not change significantly from study day to study day. Unfortunately, there is no way to know whether this is true, and if not true, to know how much variation would occur from session to session. Although we attempted to minimize the interval between sessions, ethical and practical constraints led to a 3- to 4-month interval for each volunteer's completion of the three-session study. A dose of 15 μg/kg was chosen so that plasma fentanyl concentrations could be followed for 24 h (as was necessary to accurately determine elimination half-life). It is possible that the profound physiologic effects (rigidity and hypercarbia) caused by this iv dose contributed to the inequality of fentanyl disposition between studies.

Our study is the first high-resolution pharmacokinetic study of oral transmucosal and gastrointestinal absorption of fentanyl. Comparison of the plasma fentanyl concentration *versus* time curves for OTFC and oral administration (fig. 5) shows the profound influence oral mucosal absorption plays on the movement of fentanyl into the bloodstream. Peak plasma concentrations of fentanyl after OTFC occurred 86 min before the peak concentrations after oral administration. Furthermore, peak concentrations were twice those after OTFC than after oral administration. This result is important because peak plasma concentrations relate directly to maximum drug effect. Gourlay *et al.*[12] estimated the blood concentrations of fentanyl needed for analgesia after upper or lower ab-

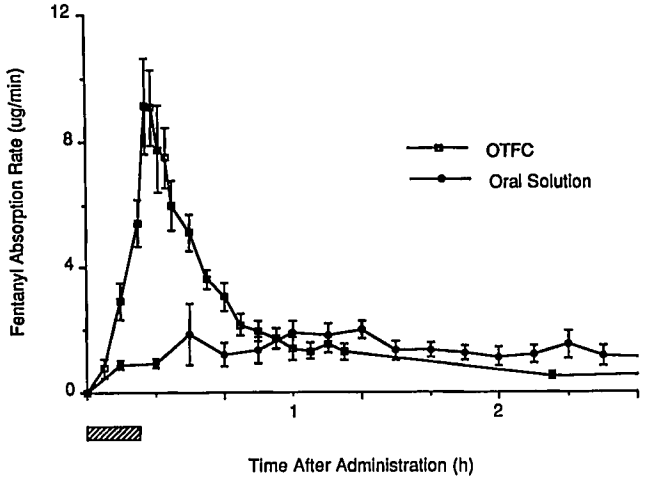

FIG. 6. Absorption rates (mean ± SEM) of fentanyl after OTFC or oral administration for the eight subjects who completed these two studies. The bar represents consumption time (15 min) for OTFC. The oral solution was swallowed within 10 s.

TABLE 3. Bioavailability of Fentanyl After OTFC and Oral Solution Administration as Determined by Two Methods

Subject	Dose-normalized AUCs*		Least-square Deconvolution*	
	OTFC	Oral Solution	OTFC	Oral Solution
1	0.48	0.47	0.44	0.45
2	0.59	0.35	0.54	0.31
3	0.49	ND	0.55	ND
4	0.42	0.25	0.47	0.23
5	0.71	0.35	0.59	0.36
6	0.52	0.42	0.53	0.37
7	0.36	ND	0.34	ND
8	0.44	0.30	0.40	0.28
9	0.37	0.19	0.37	0.17
10	0.63	0.24	0.49	0.26
Mean ± SD	0.50 ± 0.11	0.32 ± 0.10	0.47 ± 0.08	0.31 ± 0.09

ND = not done.

* See text.

dominal surgery. The *minimum* concentration found to relieve postoperative pain ranged from 0.23 to 1.18 ng/ml (mean 0.63 ng/ml).[12] Therefore, an OTFC dose of 15 μg/kg, or approximately 1 mg/70 kg, produced plasma concentrations that were consistently therapeutic for postoperative pain within 15 min of administration. These concentrations lasted for 1–2 h. Thus, an OTFC dose of 15 μg/kg might be useful for management of acute postoperative pain.

Using iv pharmacokinetic data and deconvolution analysis, it is possible to explain the plasma concentration *vs.* time profile discussed above. Absorption of fentanyl is faster and bioavailability greater after OTFC administration than after oral administration (fig. 6). The maximal rate of absorption during and after OTFC administration, approximately 10 μg/min, markedly exceeds the maximal rate of uptake possible from oral administration. Figure 7 demonstrates that the rapid rate of fentanyl absorption after OTFC administration allows approximately 150 μg of fentanyl to be absorbed within 30 min—a dose that, given iv, would be capable of producing moderate analgesia. The overall bioavailability of OTFC (50%) exceeds that of oral fentanyl (30%) because fentanyl that is swallowed undergoes moderate first-pass extraction in the liver. Because fentanyl that is absorbed transmucosally does not undergo this process, more unmetabolized fentanyl enters the systemic circulation.

Most clinical experience with OTFC has involved pediatric patients or those with cancer. Therefore, one must take care when extrapolating our results, obtained in healthy adult men, to these patient populations and to other groups who may have altered fentanyl pharmacokinetics.

Absorption of fentanyl through oral mucosal membranes is complex and involves numerous factors. During consumption of OTFC, the rate of sucking and saliva production (which is affected by the taste and *p*H of the lozenge) influences the dissolution process. Drug-laden saliva is then exposed to the absorptive surfaces of the mouth, including buccal, sublingual, gingival, and tongue mucosae. Although not specifically characterized for fentanyl, drug permeability is generally highest in the sublingual and buccal areas and lowest through the gingiva and tongue.[13] The remaining unabsorbed fentanyl is then swallowed. The amount of saliva immediately swallowed without adequate exposure to mucosal surfaces is a critical factor in overall absorption and probably accounts for much of the interpatient variability associated with OTFC delivery. In general, diffusion though biologic membranes occurs most favorably when a drug is in its nonionized, most lipid-soluble form. Ionization of fentanyl (a weak base, having a *p*Ka of 8.4[14]) depends on environmental *p*H. Higher *p*H favors the unionized form of fentanyl and enhances mucosal penetration. The *p*H in the mouth after OTFC administration results from a combination of saliva (*p*H 6.5–6.9)[15] and dissolved sucrose base (*p*H 5.5–6.0).

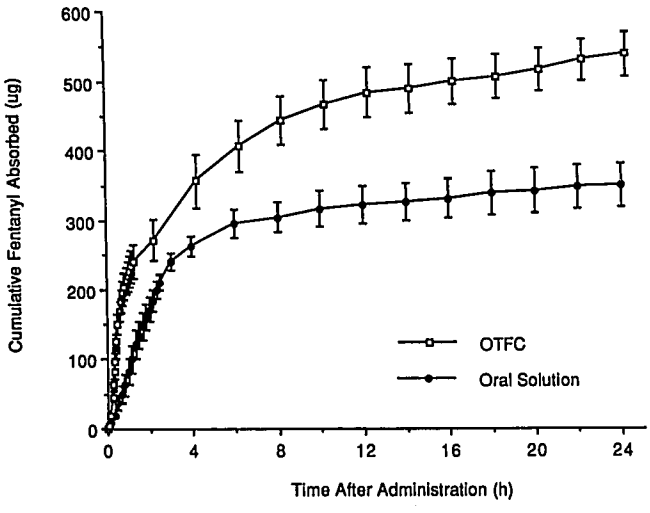

FIG. 7. Cumulative absorption of fentanyl (mean ± SEM) after OTFC or oral administration.

TABLE 4. Side Effects of Fentanyl *via* Three Routes of Administration

	Intravenous (n = 12)	Oral Transmucosal (n = 11)	Oral Solution (n = 8)
Pruritus	10	7	6
Nausea	7	3	3
Emesis	4	3	2

Values shown are the numbers of subjects experiencing each side effect.

Finally, changes in blood and lymph flow to the sites of absorption also influence transport of fentanyl into the systemic circulation.

Transdermal administration is another noninvasive form of fentanyl delivery to which OTFC administration can be compared.[10] Both the skin and oral mucosa are composed largely of stratified squamous epithelium. However, the thick, keratinous, poorly vascularized stratum corneum covering the viable epidermis of the skin impedes the absorption of fentanyl. In contrast, the epidermal lining of the mouth is thin and highly vascularized and thus more readily penetrated by fentanyl. These structural differences may also account for the markedly different values for terminal elimination half-life of fentanyl after OTFC (6.7 h) and transdermal administration (17 h).[10] Apparently, a fentanyl "depot" exists in the stratum corneum of the skin with the use of the transdermal device. However, similarity in the elimination half-life of fentanyl after iv and OTFC administration suggests that a fentanyl depot does not exist in the oral mucosa. Transdermally administered fentanyl is neither degraded by the bacteria of the skin nor susceptible to cutaneous metabolism before reaching the systemic circulation.[10] Unfortunately, the propensity for bacteria of the mouth and oral mucosa to metabolize fentanyl could not be evaluated in this study, since the total amount of fentanyl exposed to the oral mucosa was not known.

The incidence and severity of side effects in this study can be explained by comparing the rates of fentanyl input into the body and the peak blood concentrations attained with each route of administration. Muscular rigidity occurred only after iv administration. Likewise, all subjects became apneic immediately after iv infusion, whereas respiration was slowed just moderately 10–20 min after OTFC administration. Respiratory rate did not change from baseline after oral administration.

In conclusion, our data demonstrate that OTFC administration yields plasma concentrations that are higher and more rapidly attained than those after oral administration. Correspondingly, bioavailability after OTFC administration is greater than that after oral administration. This result provides compelling evidence that fentanyl from OTFC oral passes by mucosal transport directly into the systemic circulation without undergoing first-pass metabolism in the liver. Furthermore, since fentanyl elimination was not longer after OTFC than after iv administration, no fentanyl depot appears to exist in the oral mucosa.

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